

# Neural signal changes associated with cardiac and respiratory measures vs boxcar analysis in functional magnetic resonance imaging (fMRI)

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**Abstract**—Functional magnetic resonance imaging (fMRI) was used to measure signal changes in the brain during a respiratory challenge that elevated blood pressure. Subjects were scanned during a baseline period and during a Valsalva maneuver. Results were compared using fixed-effects analysis with the SPM99 package, and examined once using a boxcar model and once by models generated from changes in cardiac and respiratory signals during the breathing challenge. Models based on physiological measures resulted in greater localization of signal changes.

## I. INTRODUCTION

Determination of neural responses to blood pressure and breathing challenges is an important aspect of demonstrating brain regulation of vital functions in normal and disease conditions. Functional magnetic resonance imaging (fMRI) using the Blood Oxygenation Level Dependent [1] technique can be useful in visualizing brain areas involved in mediating cardiac and respiratory challenges [2]. Typically, physiological challenges are applied to monitor healthy neural responses to changing blood pressure. Those signal changes may be compared with responses from patients suffering from a variety of conditions, such as obstructive sleep apnea, thus assisting determination of neural mechanisms underlying the condition.

Classical fMRI study paradigms involve subjects completing a task, such as finger tapping, for a prescribed length of time, followed by a rest period; the task may be repeated a number of times. In these studies, a boxcar, or “on/off” model is typically used, with the entire challenge (“on”) time considered as a unitary period. The model has the advantage of simplicity, and allows easy comparison across subjects by averaging procedures. Neural signal changes in response to physiological challenges have been modeled previously using a boxcar model [2]. In some cases, however, a boxcar model may be inappropriate, since fMRI signal changes may be more closely related to momentary physiological alterations, or the neural responses may not follow the step function intrinsic to the boxcar design. Therefore, different models may be required to estimate neural areas of activation resulting from physiological challenges. We used respiratory and cardiac rates as independent variables in models to estimate brain signal changes of healthy subjects in response to a breathing challenge that elevates blood pressure.

## II. METHODOLOGY

Subjects were scanned using echo-planar imaging (EPI). Additional physiological data were collected. The fMRI data were preprocessed, and statistically significant signal changes were estimated using fixed effects analysis with user-specified design matrices in SPM99. A block diagram describing the experimental procedure is shown in Fig. 1.

### A. Data collection

Twenty-five volumes were collected from four healthy subjects during a 2.5 minute period. Each volume consisted of 20 oblique interleaved slices, 5 mm thick, with no interslice gap. The volume included the brain stem and cerebellum, but excluded the dorsal cortex. During scanning, various physiological signals, including respiration (thoracic wall displacement), electrocardiogram, and tissue oxygen saturation were recorded. At 1 minute into the scan, subjects performed a Valsalva maneuver (expiratory effort against a closed glottis) for the remainder of the scan. The respiratory signal, as well as breathing and

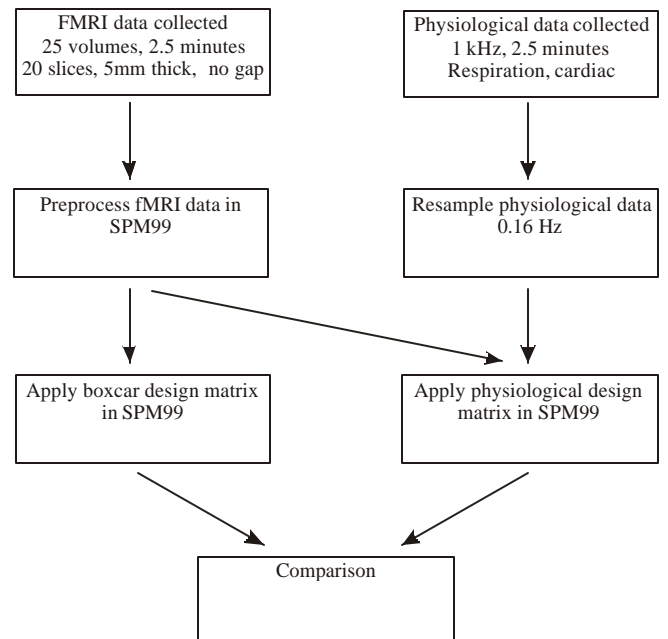


Fig. 1. Experimental procedure

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heart rates for one subject are shown in Fig. 2. The subject's breathing rate declines at the start of the challenge and heart rate increases during each Valsalva effort, declining briefly between efforts.

### B. Data processing

The fMRI data were preprocessed using SPM99. The data were initially corrected for slice timing, realigned (motion corrected) and spatially normalized. Finally, the images were smoothed using a Gaussian filter to increase the signal to noise ratio.

Statistical significance of activity was estimated in SPM99, with a design matrix as the basis for estimation. A design matrix is a model of the activity; a boxcar model convolved with a hemodynamic response function (in SPM99) was used as a first estimate of neural signal changes to the Valsalva challenge. The hemodynamic response function represents change in magnetic resonance intensity associated with blood flow changes, given a short burst of increased neural activity in a region [1]. The boxcar model assumes neural regions will have little or no signal change prior to the challenge, but express either a constant signal increase or decrease during the challenge.

Breathing rate (BR) and heart rate (HR) were calculated using a peak detection algorithm on the respiratory and oxygen saturation signals, respectively. Breathing and heart rates during scanning are shown in Fig. 3. Breathing rate approximated an inverse boxcar design. Heart rate only loosely approximated a boxcar pattern; individual differences emerged, depending principally on timing and duration of individual Valsalva efforts during the challenge.

Both rate signals were sampled once per fMRI volume (0.167 Hz), giving signals  $BR_{25}$  and  $HR_{25}$ . The  $BR_{25}$  and  $HR_{25}$  signals were sampled mid-way (3 s) into the collection period of each volume. The sampled values were used as the basis for design matrices in SPM99.

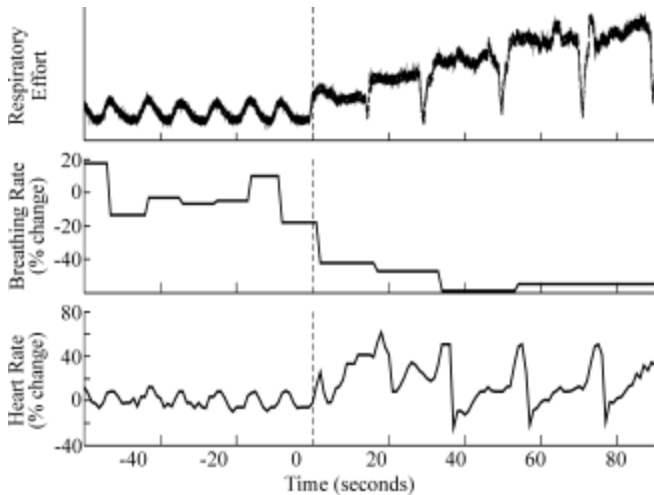


Fig. 3. Respiratory effort (top), breathing rate in percent change from baseline (middle), and heart rate in percent change from baseline (bottom) for one subject. Time 0 s represents start of challenge time (dashed line).

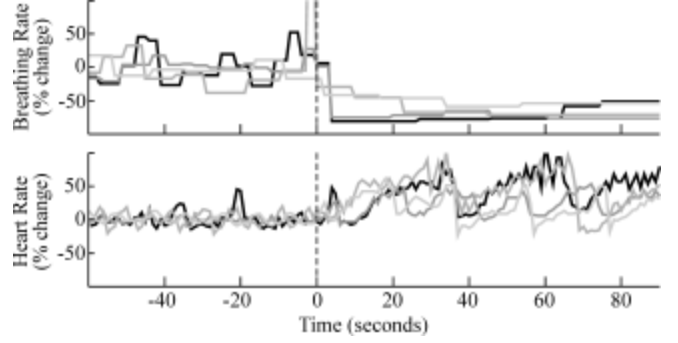


Fig. 2. Breathing rate in percent change from the baseline (top) and heart rate in percent change from the baseline (bottom) for all four subjects. Time 0 s represents start of challenge time (dashed line).

The rate design matrices identified voxels as statistically significant if their activation level was correlated to the rate. Overlapping volumes of statistically significant voxels for each of the designs were compared. The volumes were compared by creating a binary mask of the statistically significant voxels for each design and calculating the volume of overlap.

### III. RESULTS

Boxcar models resulted in broad responses, *i.e.*, dispersed signal changes in the brain, to the Valsalva challenge. A *glass brain* view of the average boxcar response for all four subjects is shown in Fig. 4. A glass brain view shows orthogonal views of a transparent brain, with projections of statistically significant regions through the brain displayed. Statistically significant regions indicate signal changes matching the shape of the boxcar model. A threshold was chosen representing the acceptable level for significance. All regions reaching the threshold are shaded gray, with more significant regions shown in darker shades.

The breathing rate model showed a similar response to that for the inverse boxcar; however, the signal changes were more localized. Those values are shown in Fig. 5.

The heart rate model showed more localized signal changes than either the boxcar or breathing models (Fig. 6), and particularly emphasizes the laterality of responses (upper right panel, Fig. 6).

Both the inverse breathing rate and heart rate models showed neural regions with enhanced signal changes in areas that correspond to regions of signal change using the boxcar model.

A comparison between the statistically significant areas of signal change for breathing rate and heart rate models showed that each model isolated different neural regions. A summary of overlapping volumes is shown in Table I. The table shows most of the statistically significant voxels indicated by the inverse breathing rate design lie within similar sites as voxels indicated by the boxcar design ( $\% \text{ Inv BR overlapping boxcar} - \% \text{ BR}^{-1}/B$ ). However, the overlap of the boxcar with the inverse breathing rate design ( $\% \text{ boxcar overlapping inv BR} - \% B/\text{BR}^{-1}$ ) is a smaller

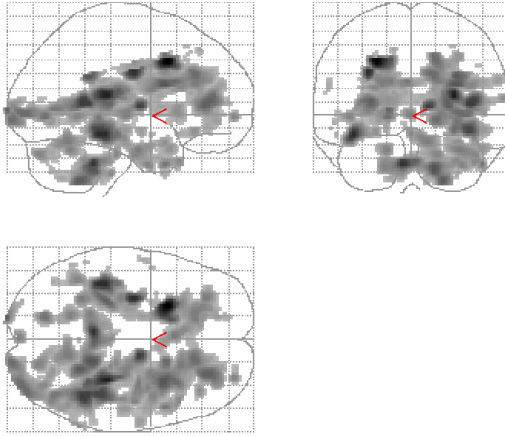


Fig. 4. Glass brain view of average boxcar response to the Valsalva maneuver for all four subjects; t-statistic shown, thresholded at 3.19, degrees of freedom 88.

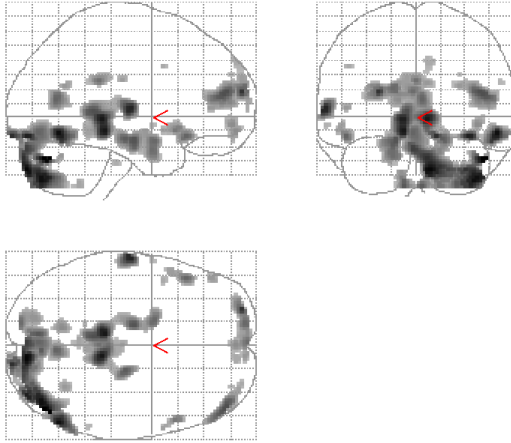


Fig. 5. Glass brain view of average breathing rate model response to the Valsalva maneuver for all four subjects; t-statistic shown, thresholded at 3.19, degrees of freedom 88.

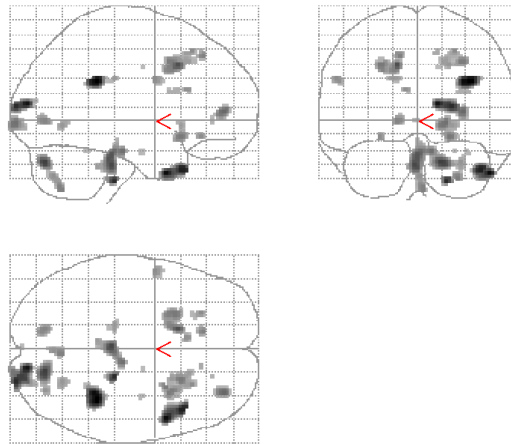


Fig. 6. Glass brain view of average heart rate model response to the Valsalva maneuver for all four subjects; t-statistic shown, thresholded at 3.19, degrees of freedom 88.

TABLE I  
Percentage (%) of volume overlap for different design matrices  
(BR = breathing rate, inv = inverse, HR = heart rate).

Subject	1	2	3	4	All Subjects
% Inv BR overlapping boxcar	81.1	83.2	22.4	75.8	96.4
% Boxcar overlapping inv BR	62.4	78.2	1.0	65.8	29.9
% BR overlapping inv boxcar	91.7	78.7	16.1	76.8	87.1
% Inv boxcar overlapping BR	69.2	89.2	2.8	80.7	65.2
% HR overlapping boxcar	28.0	42.7	8.2	12.6	55.2
% Boxcar overlapping HR	11.8	20.1	2.8	13.9	5.6

percentage of boxcar volume compared with  $\%BR^{-1}/B$ . A similar pattern emerged for overlapping areas of breathing rate and inverse boxcar designs and for overlap of boxcar and heart rate designs.

#### IV. DISCUSSION

The breathing and heart rate models allow visualization of neural activity changes directly associated with physiological output, rather than arbitrary assumptions of output associated with the boxcar model. The resulting visualization should be more likely to correspond to neural activity related specifically to control of breathing and heart rate.

The subjects induce the challenge, *i.e.* they initiate and maintain the Valsalva maneuver, rather than an external challenge being applied. Thus, separation of the neural processes associated with “initiating” rather than responding to physiological changes is an issue for consideration.

These methods should also be evaluated on challenges that are imposed, rather than initiated by the subject. A respiratory challenge such as an externally applied inspiratory load would provide an appropriate test. Since the subject would have no control over such a challenge application, the inherent variability of subject initiation of the response would diminish.

Resampling physiological data at the scan rate could introduce signal aliasing. If this were a concern, an appropriate low pass filter, such as a median filter, could be applied to the data prior to resampling.

Although the design matrices focused on breathing and heart rate in this study, other characteristics of the signals, such as momentary variability in heart rate, blood pressure, or extent of breathing effort may be applied to the creation of design matrices. For certain disease processes, such as sleep disordered breathing, such applications may be especially appropriate.

#### V. CONCLUSION

Physiological signals resampled at the same rate as fMRI data can be used as models for the statistical analysis of the fMRI data. Analysis applying physiological models may provide greater localization of signal changes related specifically to the challenge in question. Greater

localization of signal changes may allow greater specificity in identifying functionality of different brain regions.

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